10. (AMENDED) A method of selecting a molecule of interest, which is capable of binding to a target ligand, wherein the interaction between the molecule of interest and the target ligand is detected with a signal amplification system comprising:

(a) a first chimeric polypeptide comprising a first fragment of an enzyme chosen from adenylate cyclase and guanylate cyclase;

(b) a second chimeric polypeptide comprising a second fragment of an enzyme chosen from adenylate cyclase and guanylate cyclase, or a modulating substance capable of activating adenylate cyclase or guanylate cyclase, and

(c) a signal molecule precursor,

wherein the first fragment is fused to a molecule of interest, and the second fragment or the modulating substance is fused to a target ligand, and wherein the activity of the enzyme is restored by the *in vivo* interaction between the molecule of interest and the target ligand and wherein a signal amplification is generated by the restored enzyme activity; and

wherein the *in vivo* interaction occurs in a bacterial cell.

11. (AMENDED) The method of selecting a molecule of interest according to claim 10, wherein the signal amplification corresponds to production of a signal molecule.

12. (AMENDED) The method of selecting a molecule of interest according to claim 10, wherein the signal amplification triggers transcriptional activation.

13. (AMENDED) The method of selecting a molecule of interest according to claim 10, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least two distinct fragments of an enzyme.

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14. (AMENDED) The method of selecting a molecule of interest according to claim 10, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme and a modulating substance.

15. (AMENDED) The method of selecting a molecule of interest according to claim 10, wherein the target ligand is selected from proteins, peptides, polypeptides, receptors, ligands, antigens, antibodies, DNA binding proteins, glycoproteins, lipoproteins, and recombinant proteins.

16. (AMENDED) The method of selecting a molecule of interest according to claim 15, wherein the molecule of interest is capable of interacting with the target ligand.

17. (AMENDED) The method of selecting a molecule of interest according to claim 11, wherein the interaction between the molecule of interest and the target ligand is quantified by measuring synthesis of the signal molecule.

18. (AMENDED) The method of selecting a molecule of interest according to claim 11, wherein the signal molecule comprises cAMP.

19. (AMENDED) The method of selecting a molecule of interest according to claim 11, wherein the signal molecule comprises cGMP.

20. (AMENDED) The method of selecting a molecule of interest according to claim 46, wherein the reporter gene is selected from genes coding for a nutritional marker, genes conferring resistance to antibiotics, genes encoding a toxin, genes encoding a color marker, genes encoding a phase receptor protein or fragment thereof, and any other gene giving a selectable phenotype.

21. (AMENDED) The method of selecting a molecule of interest according to claim 10, wherein the molecule of interest is a mutant molecule compared to a known

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wild type molecule and said molecule of interest is tested for its capacity to interact with the target ligand.

22. (AMENDED) The method of selecting a molecule of interest according to claim 10, wherein the selection is performed in an *E. coli* strain or in any bacterial strain deficient in endogenous adenylate cyclase or guanylate cyclase.

25. (AMENDED) A method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest, wherein the stimulating or the inhibiting is detected with a signal amplification system comprising:

(a) a first chimeric polypeptide comprising a first fragment of an enzyme chosen from adenylate cyclase and guanylate cyclase;

(b) a second chimeric polypeptide comprising a second fragment of an enzyme chosen from adenylate cyclase and guanylate cyclase, or a modulating substance capable of activating adenylate cyclase or guanylate cyclase, and

(c) a signal molecule precursor,

wherein the first fragment is fused to a molecule of interest, and the second fragment or the modulating substance is fused to a target ligand, and wherein the activity of the enzyme is restored by the *in vivo* interaction between the molecule of interest and the target ligand and wherein a signal amplification is generated by the restored enzyme activity; and

wherein the *in vivo* interaction occurs in a bacterial cell, and

wherein the activity of the enzyme is tested in the presence and absence of the test substance.

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26. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least two distinct fragments of an enzyme.

27. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme and a modulating substance.

28. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the signal amplification corresponds to production of a signal molecule.

29. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 28, wherein the signal amplification corresponding to the production of a signaling molecule is blocked or partially abolished.

30. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the signal amplification generated by the restored enzyme activity leads to transcriptional activation, which leads to reporter gene expression.

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31. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 30, wherein the transcriptional activation leading to reporter gene expression is blocked or partially abolished.

32. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the target ligand is selected from receptors, ligands, antigens, antibodies, DNA binding proteins, glycoproteins and lipoproteins.

33. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the test substance is selected from proteins, glycoproteins, lipoproteins, ligands, and any other compound having stimulating or inhibitory affinity.

34. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 28, wherein the signal molecule corresponds to cAMP.

35. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 28, wherein the signal molecule corresponds to cGMP.

36. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 30, wherein the reporter gene is selected from genes coding for a nutritional marker, genes conferring resistance to antibiotics, genes encoding toxin,

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genes encoding a color marker, genes encoding phage receptor proteins or a fragment thereof, and any other gene giving a selectable phenotype.

37. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the molecule of interest is a mutant molecule compared to a known wild type molecule and said molecule of interest is tested for its capacity of interacting with the target ligand.

38. (AMENDED) The method of screening for a test substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest according to claim 25, wherein the screening is performed in an *E. coli* strain or in any bacterial strain deficient in endogenous adenylate cyclase or guanylate cyclase.

46. (NEW) The method of selecting a molecule of interest according to claim 12, wherein the transcriptional activation leads to expression of a reporter gene.

47. (NEW) The method of selecting a molecule of interest according to claim 46, wherein the interaction between the molecule of interest and the target ligand is quantified by measuring the expression of the reporter gene.

48. (NEW) The method of selecting a molecule of interest according to claim 15, wherein the molecule of interest is capable of interacting with the target ligand and of binding to the target ligand.

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